

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

In the Claims:

This listing of claims will replace all prior claims in the application.

Claims 1-23 (canceled)

Claim 24 (withdrawn) Process for the preparation of a water-

pharmaceutical formulation in solid or liquid form accord-

ing to any of claims 1 to 23 or a new product according to claims 30 to 37 and their

organic solvent-free true aqueous solutions characterized by preparation

true aqueous solutions by way of

a) dissolving the therapeutically-active compound having low aqueous solubility (<1.10-4 M/Lit, <1.10-5 M/Lit, <1.10-6 M/Lit) and a substantial binding affinity to plasma proteins ("active substance") in a water-miscible, pharmaceutically acceptable organic solvent,

b) combining said solution with the aqueous solution of the plasma protein fraction in controlled aggregation state

c) and optionally with a further pharmaceutically acceptable water-soluble auxiliary additive - such as a protein aggregation controller and/or a stabilizer -

whereby a true solution is obtained containing the said active substance and the said protein fraction bound together by way of non-covalent bonds;

d) removing the organic solvent and optionally the water preferably by ultrafiltering, dialysing, diafiltrating and/or lyophilising the solution or its concentrate or by combination of these treatments

whereby a homogeneous, water-soluble liquid or solid pharmaceutical product is obtained containing the active substance interlinked with the plasma protein fraction;

e) optionally dissolving the solid product in water or diluting the liquid product with water whereby a clear, true aqueous solution, free of any organic solvent is obtained which is suitable for therapeutic administration and

f) optionally finishing this product into a parenteral formulation (dosage form) for direct use.

Claim 25 (withdrawn) Process for the preparation of a water-soluble product or

pharmaceutical formulation in solid or liquid form according to any of

claims 1 to 23 or a new product according to claims 30 to 37 and their

organic solvent-free true aqueous solutions characterized by

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

- a) dissolving the active substance in a pharmaceutically acceptable organic solvent;
- b) combining said solution with a plasma protein fraction in controlled amounts;
- c) said solution containing the active substance and the plasma protein fraction bound together by way of a protein aggregation controller and/or a stabilizer;
- d) removing the organic solvent and lyophilising the resulting concentrate.

Claim 26 (withdrawn) A process according to step a) of any of claims 23 to 25 characterized by using to dissolve the active substance a solvent having the following properties:

- a) it is capable to completely dissolve the active substance in its mixture with water and
- b) its mixture with <50% of water does not denaturalize the protein employed.

Claim 27 (withdrawn) A process according to claim 26 characterized by using as the solvent any of the group consisting of an aliphatic C(2-4) monoalcohol or polyalcohol, 70 - 100% ethanol, dimethyl formamide, methyl formamide.

Claim 28 (withdrawn) A process according to step a) of claim 23 to 27 characterized by using as protein aggregation controller or stabilizer and/or solution stabilizing auxiliary additive any of the following agents: water, sodium chloride, a buffer, a poly- alcohol such as glycerol and/or a water-soluble sugar derivative preferably mannitol, sorbitol and/or dulcitol.

Claim 29 (withdrawn) A process according to step a) of any of claims 23 to 28 characterized by using paclitaxel and a component of the natural plasma such as serum albumin, an immunoglobulin, glycoprotein, interferon and/or interleukin or a recombinant of the same.

Claims 30-90 (canceled)

Claim 91 (withdrawn) A method of treating a human or veterinary patient in need thereof with the pharmaceutical composition of claim 1, comprising the

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

step of administering an effective amount of said pharmaceutical composition to the patient.

Claim 92 (withdrawn) The method of treatment according to claim 91 wherein the following effective amounts are administered (calculated on the therapeutically-active compound): paclitaxel and albumin 70-280 mg per treatment; propofol and albumin 6-10 mg per kG per hour; camptothecin and albumin, gemfibrozil and albumin, cyclosporin A and albumin 3-5 mg per kG per day; amphotericin B and albumin up to 1.5 mg per kG per day.

Claims 93-95 (canceled)

Claims 96-140 (not entered) *canceled*

Claim 141 (New) A pharmaceutical composition for parenteral use, comprising:

- a) a therapeutically-active compound having
  - i) an aqueous solubility of less than about  $1 \times 10^{-4}$  molar; and
  - ii) a substantial binding affinity to plasma proteins wherein greater than about 90% of the therapeutically-active compound is protein bound in spontaneous equilibrium at room temperature; and
- b) a plasma protein in controlled aggregation state selected from the group consisting of serum albumin and gamma globulin, wherein greater than about 98% of the therapeutically-active compound is non-covalently bound to the plasma protein in a water-soluble product.

Claim 142 (New) The pharmaceutical composition of claim 141, wherein the pharmaceutical composition is a water-soluble solid product.

Claim 143 (New) The pharmaceutical composition of claim 141, wherein the pharmaceutical composition is a lyophilized product.

Claim 144 (New) The pharmaceutical composition of claim 141, wherein the pharmaceutical composition is an aqueous solution.

Claim 145 (New) The pharmaceutical composition of claim 141, wherein the plasma protein is a human plasma protein.

Appl. No. 09/299,562  
Arndt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

Claim 146 (New) The pharmaceutical composition of claim 141, wherein the plasma protein is an animal plasma protein. *Claim 146*

*SLW*  
1/6/04

Claim 147 (New) The pharmaceutical composition of 141, wherein the plasma protein is a recombinant plasma protein. *Claim 147*

*SLW*  
1/6/04

Claim 148 (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is present in a mole/mole ratio to the plasma protein within the range of 1:0.05 to 1:100. *Claim 148*

*SLW*  
1/6/04

Claim 149 (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is present in a mole/mole ratio to the plasma protein within the range of 1:0.1 to 1:50. *Claim 149*

*SLW*  
1/6/04

Claim 150 (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is PACLITAXEL® and the plasma protein is human serum albumin. *Claim 150*

Claim 151 (New) The pharmaceutical composition of claim 150, wherein the therapeutically-active compound is 1 mg/ml PACLITAXEL® in absolute ethanol and the plasma protein is 20% aqueous solution of human serum albumin. *Claim 151*

*SLW*  
1/6/04

Claim 152 (New) The pharmaceutical composition of 150, wherein the therapeutically-active compound is 2 mg/ml PACLITAXEL® in absolute ethanol and the plasma protein is 4.44% aqueous solution of human serum albumin. *Claim 152*

Claim 153 (New) The pharmaceutical composition of claim 141, wherein the therapeutically-active compound is PACLITAXEL® and the plasma protein is recombinant human serum albumin. *Claim 153*

Claim 154 (New) The pharmaceutical composition of claim 153, wherein the therapeutically-active compound is 2.0 mg/ml PACLITAXEL® in absolute ethanol and the plasma protein is 4.44% aqueous solution of recombinant human serum albumin. *Claim 154*

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

SLW 1/6/04 Claim 158 <sup>Claim 1</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active drug solution is PACLITAXEL® and the plasma protein is human gamma globulin.

SLW 1/6/04 Claim 156 <sup>Claim 15</sup> (New) The pharmaceutical composition of 155, wherein the therapeutically-active drug solution is 0.1 mg/ml PACLITAXEL® in absolute ethanol and the plasma protein is 2.25% aqueous solution of human gamma globulin.

SLW 1/6/04 Claim 157 <sup>Claim 17</sup> (New) The pharmaceutical composition of claim 141, wherein the therapeutically-active compound is AMPHOTERICIN B® and the plasma protein is human serum albumin.

SLW 1/6/04 Claim 158 <sup>Claim 17</sup> (New) The pharmaceutical composition of 157, wherein the therapeutically-active compound is 4.0 mg/ml AMPHOTERICIN B® in dimethyl formamide and the plasma protein is 0.8% aqueous solution of human serum albumin.

SLW 1/6/04 Claim 159 <sup>Claim 19</sup> (New) The pharmaceutical composition of claim 141, wherein the therapeutically-active compound is AMPHOTERICIN B® and the plasma protein is recombinant human serum albumin.

SLW 1/6/04 Claim 160 <sup>Claim 19</sup> (New) The pharmaceutical composition of 159, wherein the therapeutically-active compound is 40.0 mg/ml AMPHOTERICIN B® in dimethyl formamide and hydrochloric acid and the plasma protein is 0.8% aqueous solution of recombinant human serum albumin.

SLW 1/6/04 Claim 161 <sup>Claim 19</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is camptothecin and the plasma protein is human serum albumin.

SLW 1/6/04 Claim 162 <sup>Claim 21</sup> (New) The pharmaceutical composition of 161, wherein the therapeutically-active compound is 0.14 mg/ml camptothecin in absolute ethanol and the plasma protein is 0.4% aqueous solution of human serum albumin.

SLW 1/6/04 Claim 163 <sup>Claim 21</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is camptothecin and the plasma protein is recombinant human serum albumin.

Appl. No. 09/299,562  
Amtd. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

SLW 1/6/04 Claim 164 <sup>24</sup> (New) The pharmaceutical composition of 163, wherein the therapeutically-active compound is 0.14 mg/ml camptothecin in absolute ethanol and the plasma protein is 0.4% aqueous solution of recombinant human serum albumin. <sup>Claim 23</sup>

SLW 1/6/04 Claim 165 <sup>25</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is CARBAMAZEPIN® and the plasma protein is human serum albumin. <sup>Claim 1</sup>

SLW 1/6/04 Claim 166 <sup>26</sup> (New) The pharmaceutical composition of 165, wherein the therapeutically-active compound is 8.0 mg/ml CARBAMAZEPIN® in absolute ethanol and the plasma protein is 4.0% aqueous solution of human serum albumin. <sup>Claim 25</sup>

SLW 1/6/04 Claim 167 <sup>27</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is human serum albumin. <sup>Claim 1</sup>

SLW 1/6/04 Claim 168 <sup>28</sup> (New) The pharmaceutical composition of 167, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 4.0% aqueous solution of human serum albumin. <sup>Claim 29</sup>

SLW 1/6/04 Claim 169 <sup>29</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is recombinant human serum albumin. <sup>Claim 1</sup>

SLW 1/6/04 Claim 170 <sup>30</sup> (New) The pharmaceutical composition of 169, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 2.0% aqueous solution of recombinant human serum albumin. <sup>Claim 29</sup>

SLW 1/6/04 Claim 171 <sup>31</sup> (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is human gamma globulin. <sup>Claim 1</sup>

SLW 1/6/04 Claim 172 <sup>32</sup> (New) The pharmaceutical composition of 171, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 2.25% aqueous solution of human gamma globulin. <sup>Claim 31</sup>

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

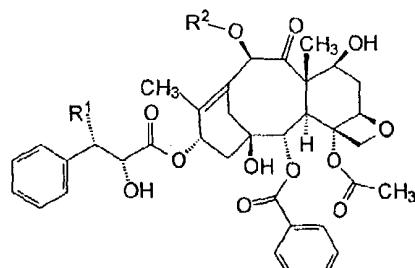
SLV 1/6/04 Claim 173 33 (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is PROPOFOL® and the plasma protein is human serum albumin. C1am 1

SLV 1/6/04 Claim 174 34 (New) The pharmaceutical composition of 173, wherein the therapeutically-active compound is 2.0 mg/ml PROPOFOL® in absolute ethanol and the plasma protein is 0.4% aqueous solution of human serum albumin. C1am 33

Claim 175 35 (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is PROPOFOL® and the plasma protein is recombinant human serum albumin. C1am 35

SLV 1/6/04 Claim 176 36 (New) The pharmaceutical composition of 175, wherein the therapeutically-active compound is 2.0 mg/ml PROPOFOL® in absolute ethanol and the plasma protein is 0.4% aqueous solution of recombinant human serum albumin.

Claim 177 37 (New) The pharmaceutical composition of claim 141, wherein the therapeutically-active compound is a taxonoid of the general formula I



wherein R<sub>1</sub> represents tert. butyl-oxy-carboxylic acid amide or benzoyl amide, and R<sub>2</sub> represents hydrogen or an acyl group.

Claim 178 38 (New) The pharmaceutical formulation of claim 177, wherein the acyl group is an acetyl group. C1am 37

Claim 179 39 (New) The pharmaceutical composition of claim 141, wherein the pharmaceutical formulation is an organic solvent-free aqueous solution.

Appl. No. 09/299,562  
Amdt. Dated September 8, 2003  
Reply to Office Action of April 8, 2003

Claim 180 <sup>40</sup> (New) The pharmaceutical composition of claim 141, wherein the pharmaceutical composition is an injectable form suitable for parenteral administration.

Claim 181 <sup>41</sup> (New) The pharmaceutical composition of claim 141, prepared by the process comprising the steps of:

- a) dissolving a therapeutically-active compound in a water-miscible, pharmaceutically acceptable organic solvent;
- b) dissolving a plasma protein in an aqueous solution;
- c) adding the organic solvent in step a) to the aqueous solution in step b);
- d) removing the organic solvent.